REMARKS

Regarding the Amendments to the Claims

Claims 5 and 11 have been amended as set forth in the above Complete Listing of the Claims. As amended, the claims are supported by the specification and the original claims. No new matter has been added. (35 U.S.C. § 132) Thus, upon entry of the amendments, claims 1-21 will be pending, of which claims 12-21 are withdrawn.

Priority Determination

It is contended in the Office Action mailed May 31, 2006 that the present application does not possess priority to the April 9, 1998 filing date of U.S. Application No. 09/058,113 (now issued as U.S. Patent No. 6,156,952), as that application does not provide support or enablement for the claimed invention. Applicants respectfully disagree.

Specifically, it is stated in the Office Action mailed May 31, 2006 that "Application 09/058113 does not disclose the combination of a human CD4/CCR5 transgenic rat or the human CD4/CXCR4 transgenic rat." The Examiner's attention is respectfully directed to the claims of the present application, in which claim 1 recites a transgenic rat with a transgene encoding CD4, as follows:

> 1. A transgenic rat, whose genome comprises at least one copy of a transgene encoding at least a portion of a CD4 protein sufficient for binding to gp120, wherein CD4 encoded by the transgene is expressed on PMBCs of the transgenic rat.

It is respectfully submitted that such a transgenic rat is disclosed, but not claimed, in priority application 09/058,113. See, for example, Example 5 (at col. 26, lines 56-64) in U.S. Patent No. 6,156,952 issued on priority U.S. Application No. 09/058,113, stating in pertinent part that:

> "A human CD4 transgenic rat can be prepared as follows. A construct containing human CD4 transgene, such as pES/CD4 (Louis Flamand; hCD4 is also described in Gillespie et al. (1993) Mol. Cell. Biol. 13:2952), containing a 6 kb Mlu 1-Sal 1 fragment (ES/CD4) with the CD4 structural gene and its regulatory sequence can be linearized and used to prepare transgenic rats using the technique of pronuclei injection described above for the preparation of the HIV transgenic rat."

Accordingly, the specification of priority U.S. Application No. 09/058,113 provides enablement and support for the CD4 transgenic rat of claim 1. The specification of priority U.S. Application

No. 09/058,113 issued as U.S. Patent No. 6,156,952 also teaches "double, triple or multimeric transgenic animals" (see the '952 patent at col. 13, line 5) and states that "[a]nimals comprising multiple transgenes can be generated by crossing different founder animals" (see the '952 patent at col. 15, lines 17-19). One exemplary multimeric animal is described at col. 11, lines 26-30 of the '952 patent, where it is stated that:

> "Transgenic non-human animals made with infectious HIV transgenes, alone or in conjunction with a transgene encoding a CD4 receptor (e.g. the human CD4 receptor) and/or an HIV co-receptor transgene (e.g. CCR5 or CXCR4) can produce infectious viral particles, which infect host cells, and therefore are particularly preferred for developing effective HIV vaccines and therapeutics." (Emphasis added.)

This description, while directed to animals that also contain an HIV transgene, clearly teaches a transgenic animal containing both CD4 and CCR5 or CXCR4. As such, the specification of priority U.S. Application No. 09/058,113 issued as U.S. Patent No. 6,156,952 provides enablement and support for claims 2-10.

Additionally, the specification of priority U.S. Application No. 09/058,113 issued as U.S. Patent No. 6,156,952 teaches that

> "[a]lthough human CD4 is essential for HIV infection, it is not sufficient. Expression of human CD4 on rodent cells renders them capable of binding virus but still nonpermissive for fusion or infection. The host component or coreceptors, sometimes referred to as the "fusion receptors", were identified only recently. These coreceptors are receptors for chemokines (i.e. small proteins which serve as chemoattractants in inflammation) and they permit HIV infection of virtually any mammalian or avian cell that expresses human CD4. The most important coreceptors are CXCR4 ... and CCR5. CXCR4 is the receptor for the chemokine SDF-1, whereas CCR5 serves as a receptor for the chemokines MIP-1α and β and RANTES. These coreceptors play a crucial function for viral entry into cells, and they are also the principal determinants of tropism among CD4+ cells." (col. 2, lines 43-63 of the '952 patent; citations omitted, emphasis added.)

As the specification of priority U.S. Application No. 09/058,113 issued as U.S. Patent No. 6,156,952 teaches CD4 transgenic rats, HIV/CD4/CXCR4 transgenic rats, HIV/CD4/CCR5 transgenic rats and the fact that coreceptors CCR5 and CXCR4 play a crucial function for viral entry into cells that also express CD4 on their surface, that specification clearly provides support

and enablement for current claims 1-10.

Furthermore, pending claim 11 of the present application recites a transgenic rat whose genome includes a gene encoding for CXCR4 and a transgene encoding at least a portion of CD4:

> 11. A transgenic rat, whose genome comprises a gene encoding CXCR4 and at least one copy of a transgene encoding at least a portion of a CD4 protein sufficient for binding to gp120, wherein CXCR4 encoded by the gene and CD4 encoded by the transgene are expressed on PMBCs of the transgenic rat.

As claimed, only the CD4 gene is necessarily a transgene. The CXCR4 may be part of the rat's natural genetic material. A transgenic CD4 rat of Example 5 of U.S. Patent No. 6,156,952 may also contain rat CXCR4. Accordingly, the specification of priority U.S. Application No. 09/058,113 issued as U.S. Patent No. 6,156,952 provides support and enablement for claim 11, which recites a CD4 transgenic rat with a genome that may include rat CXCR4.

Therefore, it is respectfully submitted that the priority date of April 9, 1998, as originally claimed, is the correct priority date for the subject matter of the presently pending claims 1-11 of the present invention. This priority date therefore is applicable to the subject matter of the claims of the present application, as the effective date for claims 1-11.

Indefiniteness Rejection Under 35 U.S.C. §112

Claim 5 has been rejected in the May 31, 2006 Office Action as allegedly indefinite, due to use of the language "the encoded transgene." As stated in the background of the specification, CD4, CXCR4 and CCR5 all play a role in mediation of entry of HIV into the host cell. The Examiner's attention is respectfully directed to amended claim 5:

> 5. The transgenic rat of claim 2, wherein the at least a portion of a CD4 protein and the at least a portion of CCR5 encoded by the transgene are capable of mediating entry of HIV.

As such, amended claim 5 clearly sets forth that both CD4 and CCR5 encoded by the transgene are involved in mediation of entry of HIV into the host cell. As claim 5 is clear and definite, and fully comports with the requirements of 35 USC 112, withdrawal of the rejection of claim 5 is respectfully requested.

Rejection of Claims 1-11 Under 35 U.S.C. §102(e)

Claims 1-11 have been rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 6,372,956 B1 (hereinafter "Goldsmith"). Applicants respectfully disagree, based on the fact that the reference is not prior art.

As stated above, the claims of the present application are entitled to the priority date of April 9, 1998. As Goldsmith was filed on December 23, 1999, it is not available as prior art to the present invention. Withdrawal of the rejection is therefore respectfully requested.

Rejection of Claims Under 35 U.S.C. §103

Claims 1-10 are rejected under 35 U.S.C. §102(e) as allegedly obvious over Browning et al. Applicants respectfully traverse the rejection.

In order for an invention to be obvious, the difference between the subject matter of the application and the prior art must be such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made. In order to meet this standard, the cited references must teach or suggest all of the elements of the claimed invention. It is respectfully submitted that Browning et al. does not teach or suggest all of the elements of the claimed invention. Specifically, Browning et al. does not teach a transgenic rat.

It is stated in the Office Action mailed May 31, 2006 that Browning et al. teaches "a bi-transgenic mouse expressing human CD4 and CCR5 that are expressed on lymphocytes and are infected by HIV-1." It is further stated that it would have been obvious to make a transgenic rat from these teachings. Applicants respectfully disagree.

While mice and rats are both rodents, they are distinctly different species. They each have a different genetic makeup, and are not directly analogous. It is noted that the rat genome is larger than the mouse genome (2.75 Gb vs. 2.6 Gb) and that only about 30% of the rat genome aligns only with mouse, a considerable portion of which is rodent-specific repeats. Of the non-aligning portion, at least half is rat-specific repeats. (*See* Rat Genome Sequencing Project Consortium, Nature, vol. 428 (2004) p. 493-521).

Accordingly, one of skill in the art would not have had motivation to combine the teachings of Browning et al, with the known teachings of transgenic rats. Due to the difference in the species of rats and mice, one of skill in the art would not have a reasonable expectation of

success in producing a transgenic rat with certain genes of a transgenic mouse. It is fundamental that a case of *prima facie* obviousness requires that "there must be a reasonable expectation of success" (MPEP 2143). As stated in MPEP 2143.02, "some degree of predictability is required." Here there is no such predictability.

The Examiner's attention in this regard is respectfully directed to the specification of the present application where it is stated that

> "...none of these transgenic mice closely model the development of AIDS in humans. In particular, none of the HIV transgenic mice express gp120 on the surface of their T cells. Thus, syncytium formation between HIV infected cells and CD4+ cells, e.g. T cells, which is reported to occur in humans and which is in fact the mechanism by which HIV is transmitted from one cell to another without the production of infectious HIV particles, does not occur in HIV transgenic mice." (emphasis added; specification, page 5.)

This failure of mice models is confirmed by the cited Browning et al. reference. The Abstract of that article states that

> "...although transgenic expression of human CD4 and CCR5 permitted entry of HIV into mouse cells, significant HIV infection was prevented by other blocks to HIV replication present in mouse cells." (emphasis added; Abstract.)

Accordingly, the CD4/CCR5 transgenic mice of Browning et al. do not model HIV and AIDS progression in humans and a need therefore remained in the art for such an animal model.

As Browning et al. does not describe a transgenic rat and one of skill in the art would not have been motivated to combine the teachings of Browning and a rat model, due to a lack of a reasonable expectation of success, Browning et al. does not render the claimed invention obvious. Accordingly, withdrawal of the rejection of claims 1-10 under 35 U.S.C. § 103 (a) as being obvious over Browning et al. is respectfully requested.

Additionally, claim 11 is rejected under 35 U.S.C. §103(a) as allegedly obvious over Sawada et al. The argument regarding lack of an expectation of success between rat and mouse models, as set forth above, is submitted as equally applicable to Sawada et al. However, as stated above, the claims of the present application are entitled to the priority date of April 9, 1998. As Sawada et al. was published in May 1998, it is not available as prior art to the present invention. Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

Based on the foregoing, all of Applicants' claims 1-11 are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

No fees are believed to be due for the filing of this paper. However, should any fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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